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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/465,491	12/16/99	CHANG	RPA1002

EXAMINER	
GOLDBERG, I	
ART UNIT	**PAPER NUMBER**
1655	7

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022829
ROCHE MOLECULAR SYSTEMS INC
PATENT LAW DEPARTMENT
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HM12/0228

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

1- File Copy

PTO-90C (Rev. 2/95)

*U S GPO 2000-473-000/44602

Office Action Summary	Application No.	Applicant(s)	
	09/465,491	CHANG ET AL.	
	Examiner	Art Unit	
	Jeanine A Enewold Goldberg	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 December 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

1. This action is in response to the papers filed December 26, 2000. Currently, claims 1-27 are pending. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow. Any objections and rejections not reiterated below are hereby withdrawn.

2. This action contains new grounds of rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 8-14, 21-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 8-14 are indefinite because the method does not provide how to quantitate telomerase activity by using the hTERT mRNA in a sample. Further it is unclear whether the quantity of telomerase activity is what is meant in the final step as telomerase activity. The final process step appears to only require determining whether there is activity, not the quantity of the activity. Thus, the metes and bounds of the claimed invention are unclear. Claims 8-14 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are directed to how the hTERT mRNA is used to quantitate telomerase activity.

B) Claims 21-27 are indefinite because the method does not provide how to identify cancerous cells by using the hTERT mRNA quantitation. The method appears to be missing steps with regard to how the hTERT is related to the cancerous cells. The method does not provide how to identify if cancerous cells are present based upon the quantity of mRNA. Claims 21-27 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are directed to how the hTERT mRNA is used to identify cancerous cells.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claim 1, 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kilian et al (Human Molecular Genetics, Vol. 6, No. 12, pg. 2011-2019, 1997) in view of Hudkins et al. (US Pat. 5,475,110, December 1995).

Kilian et al. (herein referred to as Kilian) teaches the beta deletion in the hTCS1 gene (also referred to as hTERT, see specification pg. 1). Kilian teaches that the beta-exon deletion encode truncated proteins. Kilian teaches regions surrounding the beta-exon deletion region (see Figure 5). Kilian teaches numerous oligonucleotide primers which include HT2356R. HT2356R is located within exon 8 and overlaps the last 7

nucleotides of SEQ ID NO: 4. Kilian teaches that hTCS1 is differentially expressed in normal and tumor tissues. As seen in Figure 4, TR-PCR was carried out on RNA with primer combinations including HT2356R (limitations of Claim 3). Kilian teaches southern and Northern analysis using P-labeled probes, RT-PCR analysis using electrophoresis in a agarose gel and probing with a radiolabeled oligonucleotide (pg 2017, col. 2). Finally, Kilian teaches that the beta-exon deletion encodes a truncated protein.

While Kilian teaches probing with radiolabeled probes and studying of expression levels, it is not apparent that Kilian explicitly teaches quantifying the PCR product obtained.

Hudkins et al. (herein referred to as Hudkins) teaches analysis and quantification of mRNA after separation on agarose gels. Hudkins teaches the RNA was transferred and the blots were hybridized with P-labeled probes, washed and placed in a phosphorimagining cassettes such that the density (i.e. amount of RNA) is expressed as relative pohsphorimager units (col. 19, lines 34-55).

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Kilian which detects mRNA of hTCS1 with the method of Hudkins for quantifying RNA. The skilled artisan would have been motivated to have quantitated the mRNA obtained in the method of Kilian for the expected benefit of quantifying the amount of mRNA present. Quantification of mRNA, at the time the invention was made, was a well known method which provided information regarding transcriptional activity of the mRNA and may be

used to study the expression of one gene relative to another gene. Thus, the ordinary artisan would have numerous reasons for desiring a quantitative value for the mRNA of hTERT.

5. Claims 2, 4-7, 15-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kilian et al (Human Molecular Genetics, Vol. 6, No. 12, pg. 2011-2019, 1997) in view of Hudkins et al. (US Pat. 5,475,110, December 1995) as applied to Claims 1, 3 above, and further in view of Nakamura et al (Genbank Accession Number AF015950, August 1997).

While Kilian teaches a primer which is located in exon 8 and overlaps the last 7 nucleotides of SEQ ID NO: 4, neither Hudkins nor Kilian specifically teach the primers and probes of the instant case.

Nakamura however teaches the entire sequence of the hTERT gene.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the primers of Kilan for detection of hTERT mRNA since the entire hTERT sequence was taught and characterized by Nakamura. Additionally, in the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the court determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologues, *however*, the court stated

> "Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For

example, a prior art compound may suggest its homologues because homologues often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed primers simply represent structural and functional homologues of the full length disclosed hTERT sequence concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited reference in the absence of secondary considerations. Designing primers and probes which are equivalents to those taught in the art is routine experimentation. The ordinary artisan would have been motivated to have designed probes and primers based upon the sequence of Nakurma which were functional equivalents to those provided by Kilian. Absent factual evidence that the instant primers have unexpected benefits or properties such that they would not be equivalents to those provided in the art, the claimed primers are merely functional equivalents of the primers provided in the art for amplifying the hTERT gene.

6. Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kilian et al (Human Molecular Genetics, Vol. 6, No. 12, pg. 2011-2019, 1997) in view of Hudkins et al. (US Pat. 5,475,110, December 1995) as applied to Claims 1, 3 above, and further in view of Nakamura (Science, Vol. 277, pg. 955-959, August 1997).

Neither Kilian nor Hudkins specifically teach a method for identifying the presence of cancerous cells by quantitating the hTERT mRNA.

However, Nakamura teaches that hTRT (also referred to as hTERT) is expressed in immortal (cancerous) cell strains. As seen in Figure 3, hTRT is not expressed in

telomerase-negative mortal cell lines (pg 958, col. 1). Nakamura teaches that telomerase activity was more strongly correlated with the abundance of hTRT mRNA than with that of telomerase RNA. Additionally, Nakamura teaches that the correlation of its mRNA expression level with activity also supports this conclusion (pg 958, col. 1). Moreover, Nakamura teaches that the correlation between hTRT mRNA levels and human telomerase activity shown here indicates that hTRT has promise for cancer diagnosis (pg 958, col. 3).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of quantitating mRNA as taught by Kilian and Hudkins with the teachings of telomerase activity of Nakamura. The ordinary artisan would have realized based upon the teachings of Nakamura that once the expression level of hTRT was obtained the identification of mortal versus immortal cells could be identified as provided in Figure 3 of Nakamura. Moreover, the explicit statement provided by Nakamura which teaches that the correlation between hTRT mRNA levels and human telomerase activity shown here indicates that hTRT has promise for cancer diagnosis (pg 958, col. 3).

7. Claims 22-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kilian et al (Human Molecular Genetics, Vol. 6, No. 12, pg. 2011-2019, 1997) in view of Hudkins et al. (US Pat. 5,475,110, December 1995) in view of Nakamura et al (Genbank Accession Number AF015950, August 1997) as applied to Claims 2, 4-7 above, and further in view of Nakamura (Science, Vol 277, pg 955-959, August 1997).

Neither Kilian nor Hudkins specifically teach a method for identifying the presence of cancerous cells by quantitating the hTERT mRNA.

However, Nakamura teaches that hTRT is expressed in immortal (cancerous) cell strains. As seen in Figure 3, hTRT is not expressed in telomerase-negative mortal cell lines (pg 958, col. 1). Nakamura teaches that telomerase activity was more strongly correlated with the abundance of hTRT mRNA than with that of telomerase RNA. Additionally, Nakamura teaches that the correlation of its mRNA expression level with activity also supports this conclusion (pg 958, col. 1). Moreover, Nakamura teaches that the correlation between hTRT mRNA levels and human telomerase activity shown here indicates that hTRT has promise for cancer diagnosis (pg 958, col. 3).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of quantitating mRNA as taught by Kilian and Hudkins with the teachings of telomerase activity of Nakamura. The ordinary artisan would have realized based upon the teachings of Nakamura that once the expression level of hTRT was obtained the identification of mortal versus immortal cells could be identified as provided in Figure 3 of Nakamura. Moreover, the explict statement provided by Nakamura which teaches that the correlation between hTRT mRNA levels and human telomerase activity shown here indicates that hTRT has promise for cancer diagnosis (pg 958, col. 3).

8. Claims 1, 3, 8, 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kilian et al (Human Molecular Genetics, Vol. 6, No. 12, pg. 2011-2019, 1997) in view of Hisatomi et al. (International J. of Oncology, Vol 14, pg 727-732, 1999).

Kilian et al. (herein referred to as Kilian) teaches the beta deletion in the hTCS1 gene (also referred to as hTERT, see specification pg. 1). Kilian teaches that the beta-exon deletion encode truncated proteins. Kilian teaches regions surrounding the beta-exon deletion region (see Figure 5). Kilian teaches numerous oligonucleotide primers which include HT2356R. HT2356R is located within exon 8 and overlaps the last 7 nucleotides of SEQ ID NO: 4. Kilian teaches that hTCS1 is differentially expressed in normal and tumor tissues. As seen in Figure 4, TR-PCR was carried out on RNA with primer combinations including HT2356R. Kilian teaches southern and Northern analysis using P-labeled probes, RT-PCR analysis using electrophoresis in a agarose gel and probing with a radiolabeled oligonucleotide (pg 2017, col. 2). Finally, Kilian teaches that the beta-exon deletion encodes a truncated protein.

While Kilian teaches probing with radiolabeled probes and studying of expression levels, it is not apparent that Kilian explicitly teaches quantifying the PCR product obtained. Kilian also does not teach identifying the presence of cancerous cells by hTERT quantitiy.

However, Hisatomi et al. (herein referred to as Hisatomi) teaches that levels of hTERT mRNA was investigated with regard to tumor tissue and non-cancerous tissues. The difference of hTERT mRNA level was highly significant between the tumor tissue and the non-cancerous liver tissue (abstract). Moreover, a strong correlation between

the levels of hTERT mRNA and that of telomerase activity in HCC was observed (abstract). HTERT mRNA was amplifies using primers, a real-time PCR system provided the essential information to quantify the initial target copy number (pg 728, col. 1). The levels of hTERT mRNA were provided (pg 728, col. 2) and significance was shown. As seen in Figure 2, quantification of hTERT mRNA was plotted relative to the tumor or nontumor status of the tissue (limitations of Claim 1, 21). A cutoff was provided at 1.16 such that hTERT above this "threshold" were at risk for being cancerous. As seen in Figure 4, a correlation between the quantification of hTERT mRNA and telomerase activity is provided such that telomerase activity may be assessed from the mRNA of hTERT (limitations of Claim 8).

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Kilian which detects mRNA of hTCS1 with the method of Hisatomi which quantifies the RNA expression level in log copies/ug total RNA. The skilled artisan would have been motivated to have quantitated the mRNA obtained in the method of Kilian for the expected benefit of quantifying the amount of mRNA present for utilization in expression level comparison as taught by Hisatomi. The skilled artisan would have been motivated to have quantitated the results from Kilian for analysis as provided by Hisatomi. Hisatomi teaches using the expression levels for comparing expression in cancerous versus normal cells such that data may be obtained for diagnostics such that if hTERT level is greater than the "threshold" the cells were considered cancerous.

9. Claims 2, 4-7, 9-14, 22-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kilian et al (Human Molecular Genetics, Vol. 6, No. 12, pg. 2011-2019, 1997) in view of Hisatomi et al. (International J. of Oncology, Vol 14, pg 727-732, 1999) as applied to Claims 1, 3, 8, 21 above, and further in view of Nakamura et al (Genbank Accession Number AF015950, August 1997).

While Kilian teaches a primer which is located in exon 8 and overlaps the last 7 nucleotides of SEQ ID NO: 4, neither Hisatomi nor Kilian specifically teach the primers and probes of the instant case.

Nakamura however teaches the entire sequence of the hTERT gene.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the primers of Kilan for detection of hTERT mRNA since the entire hTERT sequence was taught and characterized by Nakamura. Additionally, in the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the court determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologues, *however*, the court stated

> "Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologues because homologues often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed primers simply represent structural and functional homologues of the full length disclosed hTERT sequence concerning which a biochemist of ordinary

skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited reference in the absence of secondary considerations. Designing primers and probes which are equivalents to those taught in the art is routine experimentation. The ordinary artisan would have been motivated to have designed probes and primers based upon the sequence of Nakurma which were equivalents to those provided by Kilian. Absent factual evidence that the instant primers have unexpected benefits or properties such that they would not be equivalents to those provided in the art, the claimed primers are merely functional equivalents of the primers provided in the art for amplifying the hTERT gene.

10. Claims 1, 3, 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kilian et al (Human Molecular Genetics, Vol. 6, No. 12, pg. 2011-2019, 1997) in view of Meyerson et al. (Cell, Vol 90, pg 785-795, August 1997).

Kilian et al. (herein referred to as Kilian) teaches the beta deletion in the hTCS1 gene (also referred to as hTERT, see specification pg. 1). Kilian teaches that the beta-exon deletion encode truncated proteins. Kilian teaches regions surrounding the beta-exon deletion region (see Figure 5). Kilian teaches numerous oligonucleotide primers which include HT2356R. HT2356R is located within exon 8 and overlaps the last 7 nucleotides of SEQ ID NO: 4. Kilian teaches that hTCS1 is differentially expressed in normal and tumor tissues. As seen in Figure 4, TR-PCR was carried out on RNA with primer combinations including HT2356R. Kilian teaches southern and Northern analysis using P-labeled probes, RT-PCR analysis using electrophoresis in a agarose

gel and probing with a radiolabeled oligonucleotide (pg 2017, col. 2). Finally, Kilian teaches that the beta-exon deletion encodes a truncated protein.

While Kilian teaches probing with radiolabeled probes and studying of expression levels, it is not apparent that Kilian explicitly teaches quantifying the PCR product obtained. Kilian also does not teach identifying the presence of cancerous cells by hTERT quantitiy.

However, Meyerson teaches hEST2 (hTERT) is expressed at high levels in primary tumors, cancer cell lines, and telomerase-positive tissues, but is undetectalbe in telomerase negative cell lines (abstract). Meyerson teaches that activation of telomerase also appears to be a major step in the progression of human cancers (pg 786, col. 1). Meyerson teaches that "we analzyed the expression levels of hEST2 mRNA in various cell types, using both RNA Northern hybridizations and Rnase protection assays to do so" (pg 789, col. 2). Thus, Meyerson necessarily has quantitated the mRNA of hEST2 since an expression level was obtained. Moreover as seen in Figure 4, hEST2 mRNA was strongly expressed in a variety of cancer cell lines (pg 790, col. 1).

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Kilian which detects mRNA of hTCS1 with the method of Meyerson which quantifies the RNA expression level. The skilled artisan would have been motivated to have quantitated the mRNA obtained in the method of Kilian for the expected benefit of quantifying the amount of mRNA present for utilitzation in expression level comparsion as taught by

Meyerson. The skilled artisan would have been motivated to have quantitated the results from Kilian for analysis as provided by Meyerson. Meyerson teaches using the expression levels for comparing expression in cancerous versus normal cells such that data may be obtained for diagnostics.

11. Claims 2, 4-7, 22-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kilian et al (Human Molecular Genetics, Vol. 6, No. 12, pg. 2011-2019, 1997) in view of Meyerson et al. (Cell, Vol 90, pg 785-795, August 1997) as applied to Claims 1, 3 above, and further in view of Nakamura et al (Genbank Accession Number AF015950, August 1997).

While Kilian teaches a primer which is located in exon 8 and overlaps the last 7 nucleotides of SEQ ID NO: 4, neither Myerson nor Kilian specifically teach the primers and probes of the instant case.

Nakamura however teaches the entire sequence of the hTERT gene.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the primers of Kilan for detection of hTERT mRNA since the entire hTERT sequence was taught and characterized by Nakamura. Addtionally, in the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the court determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologues, *however*, the court stated

> "Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the

> claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologues because homologues often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed primers simply represent structural and functional homologues of the full length disclosed hTERT sequence concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited reference in the absence of secondary considerations. Designing primers and probes which are equivalents to those taught in the art is routine experimentation. The ordinary artisan would have been motivated to have designed probes and primers based upon the sequence of Nakurma which were equivalents to those provided by Kilian. Absent factual evidence that the instant primers have unexpected benefits or properties such that they would not be equivalents to those provided in the art, the claimed primers are merely functional equivalents of the primers provided in the art for amplifying the hTERT gene.

12. Claims 1, 3, 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kilian et al (Human Molecular Genetics, Vol. 6, No. 12, pg. 2011-2019, 1997) in view of Nakamura-2 et al. (Molecular Carcinogenesis, Vol 26, pg 312-320, 1999).

Kilian et al. (herein referred to as Kilian) teaches the beta deletion in the hTCS1 gene (also referred to as hTERT, see specification pg. 1). Kilian teaches that the beta-exon deletion encode truncated proteins. Kilian teaches regions surrounding the beta-exon deletion region (see Figure 5). Kilian teaches numerous oligonucleotide primers

which include HT2356R. HT2356R is located within exon 8 and overlaps the last 7 nucleotides of SEQ ID NO: 4. Kilian teaches that hTCS1 is differentially expressed in normal and tumor tissues. As seen in Figure 4, TR-PCR was carried out on RNA with primer combinations including HT2356R. Kilian teaches southern and Northern analysis using P-labeled probes, RT-PCR analysis using electrophoresis in a agarose gel and probing with a radiolabeled oligonucleotide (pg 2017, col. 2). Finally, Kilian teaches that the beta-exon deletion encodes a truncated protein.

While Kilian teaches probing with radiolabeled probes and studying of expression levels, it is not apparent that Kilian explicitly teaches quantifying the PCR product obtained. Kilian also does not teach identifying the presence of cancerous cells by hTERT quantitiy.

However, Nakamura-2 teaches that telomerase activity was examined quantitatively in gartrointestinal tissues by using the hybridization protection assay combined with the telomeric repeat amplification protocol (TRAP) to assess the diagnostic utility of measuring telomerase activity to determine the relationship between telomerase activity and human telomerase reverse transcriptase (hTERT expression) (abstract). Nakamura teaches that "the different in hTERT expression levels between cancerous and noncancerous tissues was less the mean expression level was higher in cancerous tissues than in noncancerous tissues" (pg 317, col. 1). Thus, Nakamura necessarily has quantified the hTERT levels. Moreover, using the hTERT expression levels and the plots of Figure 4, the telomerase activity may be quantitated. Finally, as provided in Figure 4, cancerous cells may be identified by their hTERT activity.

Nakamura also teaches that more than "twice higher hTERT expression in tumor than in non-tumor samples from the same patient was observed (pg 319-320).

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Kilian which detects mRNA of hTCS1 with the method of Nakamura which quantifies the RNA expression level. The skilled artisan would have been motivated to have quantitated the mRNA obtained in the method of Kilian for the expected benefit of quantifying the amount of mRNA present for utilization in expression level comparison as taught by Nakamura-2. The skilled artisan would have been motivated to have quantitated the results from Kilian for analysis as provided by Nakamura-2. Nakamura-2 teaches using the expression levels for comparing expression in cancerous versus normal cells such that data may be obtained for diagnostics.

13. Claims 2, 4-7, 22-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kilian et al (Human Molecular Genetics, Vol. 6, No. 12, pg. 2011-2019, 1997) in view of Nakamura-2 et al. (Molecular Carcinogenesis, Vol 26, pg. 312-320, 1999) as applied to Claims 1, 3 above, and further in view of Nakamura-1 et al (Genbank Accession Number AF015950, August 1997).

While Kilian teaches a primer which is located in exon 8 and overlaps the last 7 nucleotides of SEQ ID NO: 4, neither Nakamura-2 nor Kilian specifically teach the primers and probes of the instant case.

Nakamura-1 however teaches the entire sequence of the hTERT gene.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the primers of Kilan for detection of hTERT mRNA since the entire hTERT sequence was taught and characterized by Nakamura. Additionally, in the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the court determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologues, *however*, the court stated

> "Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologues because homologues often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed primers simply represent structural and functional homologues of the full length disclosed hTERT sequence concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited reference in the absence of secondary considerations. Designing primers and probes which are equivalents to those taught in the art is routine experimentation. The ordinary artisan would have been motivated to have designed probes and primers based upon the sequence of Nakamura-1 which were equivalents to those provided by Kilian. Absent factual evidence that the instant primers have unexpected benefits or properties such that they would not be equivalents to those provided in the art, the claimed primers are merely functional equivalents of the primers provided in the art for amplifying the hTERT gene.

14. Claims 17-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kilian et al (Human Molecular Genetics, Vol. 6, No. 12, pg. 2011-2019, 1997) in view of Hudkins et al. (US Pat. 5,475,110, December 1995) as applied to Claims 1, 3 above, and further in view of Nakamura et al (Genbank Accession Number AF015950, August 1997) as applied to Claims 2, 4-7, 15-16 above in further view of Stratagene Catalog (1988).

Neither Kilian, nor Nakamura specifically teach placing the primers in a kit.

However, Stratagene teaches gene characterization kits.

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have modified the oligonucleotides of Kilian and Nakamura to place the necessary reagents in kit, as taught by Stratagene, for the expected benefit of convenience and quality control. The ordinary artisan would be motivated to have packaged the primers into a kit to reduce waste, save money, increase quality control and save time, as taught by Stratagene.

Conclusion

15. No claims allowable.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Enewold Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Thursday from 7:00AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jeanine Enewold Goldberg
February 21, 2001

LISA B. ARTHUR
PRIMARY EXAMINER
GROUP ~~1800~~ 1600